IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Michael Seitz et al. Art Unit 1611
Serial No. 10/728,654
Filed December 5, 2003
Confirmation No. 8454
For MICROCAPSULES WITH AMINE ADJUSTED RELEASE RATES
Examiner Barbara S. Frazier

Declaration of David Z. Becher under 35 C.F.R. §1.132

I, David Z. Becher, declare and state as follows:

(1) I am a Senior Research Specialist for Monsanto Technology LLC. I have been a formulator for Monsanto since 1979. My responsibilities for Monsanto include the development of glyphosate (Roundup®) formulations and, relevant to the present application, the development of slow release technologies, in particular the development of herbicidal compositions comprising microencapsulated herbicidal actives. I have experience in the development of slow release, microencapsulation technologies since 1980. Finally, I am a co-author of "Microencapsulation Technology and Future Trends" published in Pesticide Formulation and Adjuvant Technology, edited by Chester Foy and David Pritchard, CRC Press, 1996.

(2) I have been asked to review and have reviewed the Final Office Action and the Advisory Action issued in connection with the present application. I have further reviewed the claims of the pending application, the disclosure of the cited Seitz et al. (U.S. 5,925,595), and the disclosure of the cited Asrar et al. (WO 2002/082901).

(3) I have also reviewed the graphical representation of half life data from Seitz et al. as presented in the Response to Final Office Action, filed with the Office on October 26, 2009 in response to the Final Office Action dated August 27, 2009. The Examiner has asserted that the graphical representation in the Response is inconsistent with the graphical representations of the data already presented by Seitz et al. I have once more reviewed the data. Based on that review, I can and do confirm that the graphical representation of the half life data is fully consistent with Seitz et al. The difference between the graphical representation of the half life data in the Response and the graphs in Seitz et al. is the presentation of additional data that Seitz et al. disclosed but did not plot.

(4) The Examiner has asserted that four of the five data points in FIG. 1 of Seitz et al. fall within the half life range taught by the applicants. It is my understanding that the disclosure of the cited reference is only relevant inasmuch as it relates to the claims. The claims require a half life of release of between 5 and 100 days. Only two of the data points in Fig. 1 of Seitz et al. are within the 5 to 100 day half life range called for in claim 1, and the graph depicted in FIG. 1 of Seitz et al. depicts six data points, not five. In fact, out of a total of 22 experiments conducted by Seitz et al. in which the half life of release was measured, only eight samples exhibited half lives of release within the ranged required in claim 1. Regardless of the number of samples having half lives falling within the claimed range, none of the samples were prepared using at least two amines.

(5) In the Advisory Action, the Examiner has perceived potentially interesting patterns in the Seitz et al. data as related to the presence or absence of a thickener. However, the person having ordinary skill in the art would not likely have drawn such a pattern from the data. A particular shortcoming in Seitz et al. that would have likely prevented the ordinarily skilled person from perceiving the patterns that the Examiner perceived is the lack of disclosure in Seitz et al. as to how the presence or absence of a thickener relates to release rate. Moreover, Seitz et al. do not describe the thickener or otherwise explain in their specification the significance of using the thickener in some formulations. That is, Seitz et al. do not describe the properties of the thickener. It is only mentioned in some of the examples, but Seitz et al. do not comment on the reason for its inclusion. Finally, to the extent that the Office has perceived an interesting correlation between the presence of a thickener and half life of release, it should be understood that correlation does not equate to causation.

(6) In any event, it cannot be ignored that whatever patterns may arguably be drawn from the Seitz et al. data they still fail to resolve the erratic, volatile character of those data. That is, as I explain more fully herein, the gross variation in release rates among Seitz et al.'s working examples cannot be attributed to the presence or absence of a thickener. If some of the variation can be attributed to the thickener, such relationship (i) would not have been either expected or perceived by one of ordinary skill in the art and (ii) cannot be explained by any evidence or theory known to me or otherwise of record in this application. Assuming hypothetically that the correlation perceived by the Examiner would have been perceived

by one of ordinary skill, it would have been dismissed as a random effect unrelated to parameters for which an effect on release rates could be rationally explained.

(7) Further to the first point in the above paragraph, the person having ordinary skill in the art would not have considered the addition of a thickener after polymerization to have any effect on the release rate. Kelzan© is the trade name for xanthan gum. Xanthan gum is highly soluble in water. Materials used to prepare the microcapsules, including the herbicidal active, the safener, the isocyanates, and the core solvent, if added, are substantially immiscible in water. I cannot perceive any condition which would cause the thickener to become incorporated into the microcapsule, either in the core or as part of the shell wall. In fact, Seitz et al. disclose that the Kelzan© xanthum gum is added to the formulation only after the microcapsules are prepared, as I further explain below.

(8) In aqueous solution, xanthan gum is a "pseudoplastic" in that an aqueous solutions comprising xanthan gum that is not subjected to any force, i.e., is at rest, is viscous. Once the solution is subject to a force, e.g., mixed or poured, the solution becomes thin. Once the force is removed, the solution become viscous again. See http://www.cpkelco.com/market_industrial/prod-kelzan.html. A common use for xanthan gum is as a thickener in salad dressing, e.g., Italian. Italian salad dressing that has not been disturbed for quite some time separates into the oil and vinegar phases. Shaking the bottle allows the two phases to mix. When the mixed bottle is at rest, the xanthan gum increases the viscosity of the mixed composition and helps keep the two phases

together. When the salad dressing is applied by pouring from the bottle, the mixed fluid pours easily. Then, when the solution is at rest on the lettuce leaves, the xanthan gum helps the viscous solution adhere to the leaves. In the same way, xanthan gum may be applied to an aqueous based herbicidal composition comprising the microcapsules that are subject of the present invention in order to render the composition viscous at rest to thereby enhance the dispersibility of the microcapsules but also allow for easy application when a force is applied through a sprayer. Its value in the formulation, such as it is, depends upon its incorporation into the aqueous phase where it can act as a pseudoplastic and thereby affect the dispersibility, pourability, and sprayability of the formulation. The Kelzan® would appear to have no role within the core of the microcapsule and would not become incorporated into either the core or the shell wall, and indeed does not.

(9) The ordinarily skilled person would not have expected the Kelzan® xanthan gum to influence the properties of the shell or the core of the microcapsules and thereby affect the half life of release because the Kelzan® xanthan gum is added to the aqueous phase of the formulation only after polymerization is complete. See Col. 15, lines 1-15 of Seitz et al., which discloses that the polymerization reaction is carried out to completion, and only after the polymerization reaction is completed, the "Formulation" is made up by adding Kelzan® xanthan gum, water, and other ingredients to the slurry. Since Seitz et al. affirmatively teach that release rates depend primarily on the permeability of the shell wall, there is no apparent way in which the thickener, present only in the aqueous phase and added only after the microcapsules are prepared, could

affect the release rate. At most, Kelzan® xanthan gum might affect mass transfer coefficients between the exterior of the cell wall and the bulk aqueous phase in which the particulate material is suspended (e.g., by increasing the viscosity of the aqueous phase). However, according to Seitz et al.'s own description of the method for determining the half life of release at Col. 11, lines 30-46, the formulation is diluted with a large enough volume of water to be treated as a perfect sink. The half life testing method therefore requires the dilution of the Kelzan® xanthan gum so significantly that its presence is merely incidental compared to microcapsule formulations that were prepared without thickener. Even before dilution, the examples indicate that the quantity Kelzan® xanthan gum added is a small fraction of the amine, isocyanate, or water. Example 16 of Seitz et al. describes preparing a formulation with the following components:

--1.17 g Kelzan® xanthan gum

--78.69 g DES N3200

--25.84 g m-TMXDI

--23.47 g TETA

--1600 g acetochlor

--about 7820 g water in the entire formulation

In this example, the concentration of the Kelzan® xanthan gum is roughly 0.015 wt.% solution compared to the total quantity of water. The half life test requires diluting 150 mg of slurry into another 1000 g water, which is stated to be a volume sufficient to act like a perfect sink. The Kelzan® xanthan gum is therefore diluted by an additional dilution factor of roughly 6667 times. In the perfect sink, the Kelzan® xanthan gum concentration is so low that the ordinarily skilled person would not have expected the gum to have any material effect on

viscosity or otherwise on mass transfer of active from the external surface of the shell walls. Moreover, even if there were an effect on mass transfer from the cell wall to the external aqueous phase, e.g., by an effect on viscosity, this would not have been expected to limit the rate of release because Seitz et al. teach that the release rate is controlled by other variables, primarily the permeability of the shell wall. Seitz nominates five variables as affecting release rates: 1) permeability of the shell wall as controlled by the ratio of isocyanates at Col. 4, line 64 to Col. 5, line 12, 2) wall thickness at Col. 1, lines 53-62, 3) nature of the active, or mixture thereof with, e.g., a safener at Col. 4, lines 21-32, 4) selection of solvent at Col. 5, lines 29-37, and 5) temperature at Col. 20, lines 1-17. All these variables have been nominated by Seitz et al. as affecting the permeability of the shell wall. No such significance is placed on the thickener. Seitz et al. do not suggest any effect of the thickener on half life; in fact, Seitz et al. offer no explanation of any purpose for the thickener in the first place.

(10) Even if the ordinarily skilled person would have perceived, like the Examiner did, a correlation between thickener and the half life of release and further if the ordinarily skilled person credited the thickener with causation, it is my view that the ordinarily skilled person would not have discovered from this realization any reason to use a blend of amines. Should an ordinarily skilled person have construed Seitz et al. in the manner suggested by the Examiner, at best it would have restored confidence in the Seitz et al. technique of preparing microcapsules with a blend of isocyanates. More directly, it would arm the ordinarily skilled person with an

entirely different weapon for controlling the release that is unrelated to the invention disclosed by Seitz et al. or the invention claimed herein. But in providing an explanation for some (but not all) of the capricious variation in half life reported by Seitz et l., attributing correlation/causation to a thickener might conceivably have restored confidence in the Seitz et al. scheme of varying the isocyanate ratio, from which the artisan would otherwise have been deterred by inspection of the data.

(11) However, a careful review of the Seitz et al. data reveals that contrary to the Examiner's assertions, the use of a thickener does not have any consistent or predictable effect on half life of release. Example 16 of Seitz et al. is comparable to Example 13 of Seitz et al. In Examples 13 and 16, the ratio of Desmodur N3220 to TMXDI is 67%:33%. Example 17 of Seitz et al. is comparable to Example 14 of Seitz et al. In Examples 14 and 17, the ratio of Desmodur N3220 to TMXDI is 80%:20%. In Examples 16 and 17, thickener was added to the slurry to make up the Formulation. Examples 13 and 14 were formulated without thickener. The ratio of half life of Example 16 (thickener) to Example 13 (same formulation but no thickener) is 1.83:1. The ratio of half life of Example 17 (thickener) to Example 14 (same formulation but no thickener) is 11.3:1. Therefore, if causation is to be assumed, the thickener increased the half life of release by about 80% when used in one sample, but increased the half life by more than an astounding 1100% in another sample. If the thickener is assumed to have caused the increase in half life, these data do not allow any predictability as to the extent of the increase, and Seitz et al. provided no disclosure whatsoever to explain these

differences or in any way resolve the large degree of variation. Additionally, none of samples in Examples 7-12, which were used to construct the graph on page 28 of the Office Action Response, employed a thickener, and the data are still erratic. No explanation is given in Seitz et al. for the erratic nature of these results, and the erratic nature of these results cannot be attributed to the thickener since no thickener was used in any of the Examples 7-12.

(12) Seitz et al.'s use of a blend of two isocyanates results in microcapsules exhibiting a high degree of volatility in terms of half life. In the graphical representations submitted in the Response to Final Office Action, I observe precipitous slopes in half life vs. composition curves, which is prevalent in both: a) formulations that contain no thickener and b) formulations that contain a thickener. For example, the table and graph on page 27 of the response to the August 27, 2009 Final Office Action shows very steep increasing slope, i.e., a dramatic increase in half life, from Example 2 (50%:50% ratio) to Example 3 (33%:67% ratio), and then a very sharp decrease in slope, i.e., a dramatic decrease in half life from Example 3 to Example 4 (10%:90%). There is thus large variation in half life over relatively little compositional change. I observe the same volatility in the graph on page 28 of the response to the August 27, 2009 Finally Office Action. The latter comparisons were made in samples that did not contain thickener.

(13) Seitz et al. recognized that all the amines that were listed in their disclosure have the same function, which was to react with the isocyanate functionality present on the

isocyanate molecules. Seitz et al. further enabled the ordinarily skilled person to predict that each of these individual amines would function adequately. However, Seitz et al.'s disclosure and data would not have made it predictable that the use of a primary amine and an auxiliary amine at varying ratios would provide superior control of the release rate. In contrast to the graphical presentations of the Seitz et al. data, the half life release values for the formulations of the present invention are smoothly and reliably correlated to the relative proportions of principal and auxiliary amines, and the half lives fall in a useful range over wide ranges of relative proportions, as shown in the chart on page 29 and the graph on page 30 in the Response to the August 27, 2009 Final Office Action. In reviewing the various graphical presentations of data in that Response, it is critical to note that the half lives are given in hours and the scale extends to just 700 hours in the graph plotting the applicants' compositions on page 30, while the scale extends to 60,000 *days* in the graph plotting Seitz et al.'s compositions on page 28. 60,000 days is 1,440,000 hours. Accordingly, the scale of the graph on page 28 is over 2000x the scale of the graph on page 30. The scale of the graph on page 27 is to 14,000 hours, which is still 20x the scale of the graph on page 30.

(14) It is important to keep these differences in scale in mind if one is to compare the Seitz et al. data with the half lives of release obtained from the microcapsules of the present application, which were prepared using a blend of a principal amine and an auxiliary amine. The data are directly comparable since the difference between the half lives and their reproducibility result from the substitution of a polyisocyanate

with a polyamine. A comparison of these data yields the following conclusions, among others, regarding the exceedingly and unexpectedly superior control of half life of release obtained by using a blend of amines over a blend of polyisocyanates:

(15) First, the half lives of release of the Seitz et al. examples vary widely with relatively minor changes in the relative proportions of the polyisocyanates. Compare this to the half lives of release of the present application's examples, which show far less variability in half life with any given increment of change in the relative proportions of polyamines. Nothing in Seitz et al.'s disclosure would have given the ordinarily skilled person the ability to predict that the half life of release could be so reliably controlled by varying the relative proportion of the amines in a polyamine blend. This is thus one unexpected benefit of using a principal amine and an auxiliary amine to prepare the microcapsule shell wall.

(16) Second, many of the half lives of release of the Seitz et al. examples are excessively long and thereby result in commercially impractical pesticidal materials. Some of the examples had measured half lives on the order of *years* (e.g., 16 years, 56 years, and even 95 years for Seitz et al.'s examples 8-10).[1] The data show that only minor variations in the relative ratio of polyisocyanates can alter the release rate characteristics widely from short half lives to exceedingly long

[1] While some of these half-lives were extrapolated out to very long durations and thus may involve some experimental or theoretical error in their measurement and calculation, particularly since it is impossible to measure a half live of 95 years in a practical manner, nevertheless, it is safe to conclude that the half-lives of certain of the Seitz et al. microcapsules are significantly longer than a half life that is commercially useful.

half lives. Only a select window of polyisocyanate proportions yields microcapsule release rates of commercially acceptable durations using Seitz et al.'s method. Given the steep rate of change in half life versus isocyanate ratio, one skilled in the art would have very little confidence that the acceptable window would be reproducible. In the present application, the entire range of polyamine blends yield commercially useful microcapsule release rates. For example, over the entire range of relative proportions of amines, the half life varies from about 1 day to about 26 days. Significantly, modest variation in amine ratio does not throw the release rate out of control. Depending upon soil conditions, climate, the crop, the types of weeds that may be present, etc., a commercial use may be found for each and every example of the inventive pesticidal material. This contrasts sharply with Seitz et al., whose examples show only a few of the microcapsules (e.g., some of the microcapsules having less than 10% N3200 or greater than 80% N3200) have half lives of comparable duration, and the extreme sensitivity of half life to small changes in proportions makes quality control difficult, if not impossible. Nothing in Seitz et al.'s disclosure would have given the ordinarily skilled person the ability to predict that the entire range of relative proportions of the amines in a polyamine blend yield commercially viable pesticidal materials while only select, narrow and potentially unstable windows of proportions of isocyanates result in commercially viable controlled release materials using the Seitz et al. method. Therefore, this is another unexpected benefit of using a principal amine and an auxiliary amine to prepare the microcapsule shell wall.

(17) Throughout the course of examination, including the Advisory action, the Examiner has consistently relied on Asrar et al. '901 as central to the argument that the use of a blend of amines would have been obvious. In the absence of Asrar et al., one skilled in the art could not have been led to either: (a) depart from the concept of Seitz et al. by using a blend of different amines to control release rate or (b) use the concept of Seitz et al. as a starting point for improving the control of release rates. It is my understanding that there are legal reasons why the disclosures of Asrar et al. '901 should not be considered prior art against the claims of the above-designated application.

(18) In conclusion, it is agreed that Seitz et al. teach that the ratio of two isocyanates may be varied to control permeability. However, Seitz et al. do not disclose or suggest departing from that concept and using a blend of amines for the purpose. It is also agreed that the release rate can be modified by, e.g., adding solvents to the core or other materials such as safeners. However, one skilled in the art would not have perceived this as leading to the entirely different concept of using a blend of amines for the shell. Finally, it is also agreed that two components can be released at different rates, depending on their solubility and molecular size. However, this does not suggest to one skilled in the art the entirely different concept of using a blend of amines to control release rate. It may even be the case that a thickener in the formulation slurry may affect release rates (but see the above discussion in which I point out the reasons why this is probably not so). But again, the use of a thickener does not suggest to one skilled in the art the entirely different concept

of using a blend of amines to control release rate. It is my view therefore that Seitz et al. neither disclose nor suggest the use of a principal amine and an auxiliary amine in the preparation of polymers useful as microcapsule shell wall materials nor does Seitz et al.'s disclosure provide any reasonable expectation that the use of a blend of amines enables superior control of the release rate properties of microcapsules prepared thereby.

(19) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

David Z. Becher — 1/14/2010

David Z. Becher — Date